Systematic Review or Meta-analysis

Incidence of sight-threatening diabetic retinopathy in people with Type 2 diabetes mellitus and numbers needed to screen: a systematic review

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Abstract

Aim   To investigate the incidence of sight-threatening diabetic retinopathy in Type 2 diabetes mellitus.

Background   In most countries, yearly or biennial screening intervals for diabetic retinopathy in people with Type 2 diabetes are recommended. Fewer screening sessions reduce the effort required of people with Type 2 diabetes and reduce healthcare costs.

Methods   We conducted a search of PubMed, Embase, Web of Science and the COCHRANE Library for studies published betweeen 1 January 2000 and 1 January 2017. Eligible studies were those that included general populations of >100 people with Type 2 diabetes mellitus. Additional study population criteria were absence of moderate diabetic retinopathy or more severe diabetic retinopathy at last screening session and at least two gradable retinal screening sessions. Outcomes of interest in the included studies were moderate and severe non-proliferative diabetic retinopathy (R2), proliferative diabetic retinopathy (R3) or maculopathy (M1), collectively known as sight-threatening or referable diabetic retinopathy.

Results   A total of 17 studies were included. In people with Type 2 diabetes without or with only mild diabetic retinopathy at baseline, the average incidence rates of sight-threatening diabetic retinopathy were ~1 per 100 person-years and ~8 per 100 person-years, respectively. The average numbers needed to screen to detect one case of sight-threatening diabetic retinopathy were 175 and 19 in people without and with mild retinopathy at last screening, respectively.

Conclusion   In people with Type 2 diabetes without retinopathy at last screening, the incidence of severe sight-threatening retinopathy at the subsequent screening session was low. In people with mild retinopathy, progression to sight-threatening diabetic retinopathy was nearly 10-fold higher. This review supports lengthening of the screening interval of patients with Type 2 diabetes without retinopathy at last screening session.

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Introduction

Diabetic retinopathy is a chronic, potentially sight-threatening complication of diabetes mellitus that can be detected by periodic screening of the fundus. For the classification of diabetic abnormalities, two grading schemes are used: the Early Treatment Diabetic Retinopathy Study classification (ETDRS) and the more recent National Screening Committee (NSC) [1,2]. Absence of diabetic retinopathy is classified as '10' (ETDRS) or 'R0' (NSC). Aneurysms and small retinal haemorrhages may progress to mild, non-proliferative diabetic retinopathy or background diabetic retinopathy (ETDRS 20–35, NSC R1), or to moderate to severe non-proliferative diabetic retinopathy (ETDRS 43–53, NSC R2), and ultimately to proliferative diabetic retinopathy (ETDRS ≥61, NSC R3) [1,2]. It is estimated that this progressive pattern takes on average ~17 years [3,4]. Regression from mild non-proliferative diabetic retinopathy (R1) to no visible retinopathy occurs

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What's new?

- The incidence of sight-threatening diabetic retinopathy (STDR) in people with Type 2 diabetes is decreasing, probably as a result of improving diabetes care.

- In screen-detected mild retinopathy (R1), regression to no visible retinopathy (R0) is common.

- In people with mild retinopathy at baseline, development and detection of STDR by the time of the next screening visit is nearly 10 times more frequent than in people without retinopathy at baseline.

- Recent data on incidence and numbers needed to screen can be helpful in constructing optimal intervals for the screening of the large population of people with Type 2 diabetes with no or only mild retinopathy.

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in up to 46% of cases [3,5–8]. This regression is reinforced by effective treatment of hypertension and hyperglycaemia [3,9].

Diabetic maculopathy or macular oedema (NSC M1) represents a spectrum of retinopathy symptoms characterized by oedema, fine macular exudates with or without haemorrhages and thickening of the central macula and surrounding non-central macula. The gradings R2, R3 and M1 are classified as sight-threatening diabetic retinopathy (STDR) or referable diabetic retinopathy.

Proliferative diabetic retinopathy (R3) is an urgent sight-threatening condition, which needs a fast-track referral for ophthalmological treatment to prevent loss of vision. All screen-detected STDRs need comprehensive diagnosis, monitoring, and eventually treatment by an ophthalmologist. Timely screen detection of STDR and referral and treatment can prevent or slow down loss of visual acuity.

The incidence of STDR has decreased over the last decades [10,11]. Between 1991 and 2006, the screen-detected prevalence of all referable diabetic retinopathy (R2 or R3 or M1) cases increased from 2.0% to 4.7% in the UK, but in that period the prevalence of the most severe STDR (R3 or M1) dropped by 91%: from 1.7% to 0.16% [12]. Several authors suggest extending the screening interval for people with Type 2 diabetes without retinopathy at last screening session [13–16] to 2 [12,17] or 3 years [18–20].

We present a systematic review of current population-based screen-detected incidences and numbers needed to screen for STDR in Type 2 diabetes to contribute to the discussion concerning the length of the diabetic retinopathy screening interval in people with Type 2 diabetes. The questions addressed are: (1) the incidence of moderate to severe non-proliferative diabetic retinopathy, proliferative retinopathy and diabetic maculopathy (STDR) in people with Type 2 diabetes without pre-existing diabetic retinopathy or with only background or mild non-proliferative diabetic retinopathy at baseline, and (2) the number of

screening sessions needed to detect one case of severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy and diabetic maculopathy (STDR) in people with Type 2 diabetes without diabetic retinopathy or with only background or mild non-proliferative diabetic retinopathy at baseline.

Participants and methods

Eligibility criteria

We searched for studies published between 1 January 2000 and 1 January 2017, in the English language, whose outcomes were incidence of severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy, diabetic maculopathy, referable diabetic retinopathy or STDR. The study samples were general populations with Type 2 diabetes ($N > 100$), not participating in a diabetes-related trial, who had no diabetic retinopathy (ETDRS 10 or NSC R0) at last screening session, i.e. at baseline, or only minimal background or non-proliferative diabetic retinopathy (EDTRS >10 and <35 or NSC R1) at last screening, i.e. at baseline. The study populations were required to have undergone at least two gradable retinal screening sessions.

Information sources

The literature search was performed by an expert librarian on 3 January 2017. Databases searched were PubMed, Embase, Web of Science and the COCHRANE Library.

Search strategy PubMed

Search terms used were: (((("STDR"[tiab] OR (("Diabetic Retinopathy"[mesh] OR (("diabetic"[all fields]) AND ("retinopathy"[all fields] OR ("macular oedema") OR "maculopathy"[all fields] OR "CSME"[all fields] OR "retinopathies"[all fields]))) AND ("sight threatening"[all fields] OR "sight-threatening"[all fields] OR "progressive"[All fields] OR "proliferative"[all fields] OR "referable"[all fields]))) AND ("Incidence"[Mesh] OR "incidence"[all fields]))). The filters applied were English language and publication date range from 1 January 2000 to 1 January 2017.

Selection of publications and extraction of data

Two authors (Y.G. and D.T.) selected the papers independently. Papers were screened for eligibility by title and, if necessary, by examining the abstract. No systematic reviews were found in the literature search. Only a few discrepancies in the selections of the two authors occurred. These were discussed and consensus was reached in line with our search criteria. We contacted the corresponding authors of three papers. One author group provided non-published data on the number of screening sessions,

Table 1 Screening studies reporting incidence of sight-threatening diabetic retinopathy in Type 2 diabetes 2000–2017

Author	Publication year	Location	Study period	Duration of follow-up, years	Screening interval, years	Screening method, per eye	Mean ± SD age (years) at first screening	Mean ± SD diabetes duration (years) at first screening	Mean HbA1c or FBG at first screening, mmol/(%)	Participants without diabetic retinopathy at first screening	Participants with mild diabetic retinopathy at first screening
Stratton et al. [21]	2001	England, UK	1983–	6	3	Retinal photographs, not specified	52.2 ± 8.5	0	53 ± 12.9 (7.0 ± 1.7)	1216	639
Younis et al. [18]	2003	England, UK	1991–1999	5	1.5	Three overlapping photographs	63.4 ± 6.9	3.0	-	3743	810
Leske et al. [24]	2006	Barbados	1992–1999	5	4.6	Standard fundus photographs of fields 1 and 2 (ETDRS 1985)	61.9	7.3 ± 7.4	94 ± 12 (10.8 ± 3.3)	324	-
Cikatamana et al. [25]	2007	Australia	1987–2003	9	4.5	Stereo- and non-stereo photographs of five fields	57.6 ± 9.4	5.8 ± 7.5	FBG 8.1 ± 3.3	97	39
Olafsdottir and Stefansson [17]	2007	Iceland	1995–2005	10	2	Slit-lamp with a 90-diopter lens and colour photographs	-	-	-	199	-
Sloan et al. [22]	2008	USA	1999–2006	6	1	Unknown	74.8 (only 65+ patients)	-	-	30,722	-
Agardh and Tababat-Khani [19]	2011	Sweden	2006–2009	3	3	Two 50° red-free fundus photographs	60 ± 12	6 ± 6	46 ± 10.8 (6.4 ± 1.5)	1691	-
Song et al. [5]	2011	Hong Kong	2005–2009	4	1	Nine 45° field digital fundus photographs	62.6 ± 9.6	-	-	3647	1387
Thomas et al. [15]	2012	Wales, UK	2005–2009	4	1.36	Two 45° digital retinal images	64.4 ± 11.3	4.2 ± 4.4	-	49 763	-
Jones et al. [14]	2012	England, UK	1990–2006	17	1.5	Two photographs	66.7	2.5	-	16 444	3632
Looker et al. [7]	2013	Scotland, UK	2005–2011	5	1.05 (1.01-1.16)*	Photography (if ungradable: slit lamp)	64.4 ± 11.8	4.1 (1.6–7.5)*	56 ± 17 (7.3 ± 1.5) without DR 60 ± 17 (7.6 ± 1.6) with mild DR	101 539	35 227
Scanlon et al. [20]	2013	England, UK	2005–2011	3.4	1.125	Two field 45° digital retinal images	66 (57–74)*	-	-	12 491	6553
Liu et al. [3]	2013	Scotland, UK	1990–2011	21	1	Single-field 45-degree retinal photographs	-	0.5	55 (7.2); longitudinal mean	4662	-
Salinero-Fort et al. [26]	2013	Spain	2008–2011	4	1	Slit lamp biomicroscopy	67.8	7.7 (7.1)	53 ± 12 (7.0 ±1.1)	2405	-
Martin-Merino et al. [27]	2014	UK	2000–2007	9	-	Unknown	Diabetes onset 61.3	0	-	63 226	-
Van der Heijden et al. [23]	2014	Netherlands	1998–2010	4.4	2.5	Two 45° photographs	60.5	1.35	60 (7.6)	2980	302
Yun et al. [4]	2016	South Korea	2001–2005	11.8 (9.8–13.2)*	1	One 45° fundus photograph	54.3 ± 10.0	6.7 ± 3.5	66 ± 13 (8.2 ± 1.2)	523	-

FBG, fasting blood glucose. *Interquartile range.

Table 2 Number of people with Type 2 diabetes without diabetic retinopathy at baseline and number of events and incidence rate of screen-detected sight-threatening diabetic retinopathy during follow-up per 100 person-years or per 100 screening-sessions

Author	Person-years or screening-sessions	R2 level Number, incidence rate (95% CI)	R3 level Number, incidence rate (95% CI)	M1 Number, incidence rate (95% CI)	Incidence rate per 100 person-years or 100 screening- sessions (95% CI)
Younis et al. [18]	13,053		76 0.58 (0.5-0.7) ETDRS ≥ 40	58 0.44 (0.3-0.6)	1.02 (0.9-1.2)
Sloan et al. [22]	31,722	-	63 0.2 (0.2-0.2)	124 0.39 (0.4-0.4)	0.59 (0.57-0.62)
Jones et al. [14]	57,385		763 1.33 (1.2-1.4)		1.33 (1.2-1.4)
Looker et al. [7]	300,817*		282 0.1 (0.1-0.1)	1605 0.5 (0.5-0.6)	0.6 (0.6-0.7)
Liu et al. [3]	36,574		100 0.27 (0.2-0.3) ETDRS ≥ 53	-	0.27 (0.2-0.3)
Salinero-Fort et al. [26]	7,984	11 0.14 (0.1-0.2)	68 0.85 (0.7-1.1)	30 0.38 (0.3-0.5)	1.37 (1.1-1.6)
Martin-Merino et al. [27]	282,850	-	-	885 0.30 (0.3-0.3)	0.30 (0.3-0.3)
Yun et al. [4]	2,092		32 1.5 (1.0-2.2)	-	1.5 (1.0-2.2)

ETDRS, Early treatment diabetic retinopathy study.
*Screening-sessions.

Table 3 Number of people with Type 2 diabetes with diabetic retinopathy at baseline, number of events during follow-up and incidence rate of screen-detected sight-threatening diabetic retinopathy during follow-up per 100 person-years or per 100 screening-sessions

	Person-years	Retinopathy status at first screening R1	R2 Level Number, incidence rate (95% CI)	R3 level Number, incidence rate (95% CI)	Maculopathy M1 Number, incidence rate (95%CI)	Incidence rate per 100 person-years or 100 screening- sessions (95% CI)
Younis et al. [18]	2,795	Background DR ETDRS 20-40	150 5.4 (4.6-6.3) ETDRS > 40		127 4.5 (3.8-5.4)	9.9 (8.8-11.2)
Jones et al. [14]	8,443	NPDR		475 5.63 (5.1-6.2)		5.63 (5.1-6.2)
Looker et al. [7]	104,133*	Mild background DR	808 0.8 (0.7-0.8)		4,457 4.3 (4.2-4.4)	5.1 (5.0-5.2)

DR, Diabetic retinopathy; ETDRS, Early treatment diabetic retinopathy study; NPDR, Non-proliferative retinopathy; PDR, Proliferative retinopathy; STDR, Sight threatening diabetic retinopathy.
*Screening-sessions.

which we used in the present review [14]. Two author groups did not answer repeated requests for information. Their papers were not included because interpretable data were missing.

Outcomes

We report the yearly incidence of STDR in systematically screened, non-selected people with Type 2 diabetes, free from screen-detected retinopathy (R0) or maculopathy (M0) or with minimal screen detected retinopathy (R1) at last screening session, as well as the resulting numbers needed

to screen to detect one case of STDR. The incidence rates of STDR are calculated as incidence rate per 100 person-years or as mean cumulative incidence per 100 participants per year of follow-up.

Baseline participant characteristics are provided where these were reported in the included studies.

Statistical analysis

Incidence rates

If the study mentioned the yearly number of people at risk plus the yearly number of detected retinopathy cases,

incidence was presented as incidence rate. 'Incidence rate' was numerically defined as the number of new cases of severe diabetic retinopathy within a time period, as a proportion of the number of people at risk of severe diabetic retinopathy.

If only the number of yearly screening sessions was presented, we equated these with person-years [7]. Incidence rates are presented in Tables 2 and 3.

Cumulative incidence

If yearly numbers of people at risk were not available, cumulative incidence over the study period was calculated; therefore, we divided the total number of incident cases by the number of participants. Taking into account the duration of the study follow-up, the mean yearly cumulative incidence is reported in Tables 4 and 5. For duration of follow-up we took the total length of follow-up, if this was equal for all included participants, or the median length of follow-up for studies in which the follow-up varied.

Confidence intervals of incidence rates were calculated using the Rothman/Greenland formula, and confidence intervals of cumulative incidences using the Wilson formula.

If the number of screening sessions was presented in the study, the quotient of screening sessions and detected STDR cases during these sessions was used to calculate the number needed to screen to detect one case of STDR. The mean numbers needed to screen are presented as weighted means. For each study, we therefore used the total number of screen-detected STDR cases as value and the total number of screening sessions as weight (http://www.thinkcalculator.

com/statistics/weighted-mean-calculator.php; Tables 6 and 7).

Results

Of the 692 unique records that were identified in the systematic search, 51 qualified for full-text evaluation (Fig. 1). A total of 17 studies met the inclusion criteria (Table 1 [3–5,7,14,15,17–27]). Fourteen studies were based on predominantly white populations in one of 10 different Western countries. One study described a population in South Korea, one in Hong Kong and one in Barbados. Nine studies reported the incidence of STDR in participants without diabetic retinopathy at last screening session and eight studies also documented people with only mild non-proliferative diabetic retinopathy at last screening session. Most data were derived from screening programmes. The mean age of the participants varied among studies from 52.2 [21] to 74.8 [22] years. Glycaemic control of the participants, as far as reported, was good to moderate except for hyperglycaemia in the Barbados cohort.

The screening interval varied from 1 to 10 years and study duration from 3 to 17 years (Table 1).

Tables 2 and 4 present the incidence of STDR in people with Type 2 diabetes without diabetic retinopathy at last screening session. Tables 3 and 5 present the incidence of STDR in people with Type 2 diabetes with only mild non-proliferative diabetic retinopathy at last screening session.

Table 4 Number of people with Type 2 diabetes without diabetic retinopathy at baseline, number of events and cumulative incidence of screen-detected sight-threatening diabetic retinopathy during follow-up per year

Author	Partici-pants	R2 Level Number, Cumulative incidence (95% CI)	R3 level Number, Cumulative incidence (95% CI)	Maculopathy M1 Number, Cumulative incidence (95% CI)	Cumulative incidence of sight threatening diabetic retinopathy per year of follow-up (95% CI)
Stratton *et al.* [21]	1,216	17 1.4 (0.9-2.2)	1 0.1 (0.0-0.5)	–	0.25 (0.1-0.7)
Leske *et al.* [24]	324	9.0 (5.5-12.4)	2.6 (1.0-4.3)	8.7 (5.4-12.0)	0.92
Cikamatana *et al.* [25]	90	0	0	–	0 (0-4.1)
Olafsdottir and Stefansson [17]	199	12 6.03 (3.5-10.2)	2 1.01 (0.3-0.6)	4 2.01 (0.8-5.1)	0.91 (0.3-3.6)
Agardh and Tababat-Khani [19]	1,322	–	0	3 0.23 (0.1-0.7)	0.08 (0.0-0.4)
Song *et al.* [5]	3,647	25 0.69 (0.5-1.0)	5 0.14 (0.1-0.3)	–	0.21 (0.1-0.4)
Thomas *et al.* [15]	49,763	126* 0.25 (0.2-0.3)	28 ** 0.06 (0.0-0.1)	197 0.40 (0.3-0.5)	0.19 (0.1-0.2)
Scanlon *et al.* [20]	12,491	74*** 0.59 (0.5-0.7)	9 0.07 (0.0-0.1)	361 2.89 (2.6-3.2)	1.04 (0.9-1.2)
Van der Heijden *et al.*	2,980	–	311.0 (0.7-1.5)		0.22 (0.1-0.5)

*16 patients had also maculopathy.
**3 patients had also maculopathy.
***R2 or R3.

Table 5 Number of people with Type 2 diabetes with diabetic retinopathy at baseline, number of events and cumulative incidence of screen-detected sight-threatening diabetic retinopathy during follow-up per year

Author	Participants	Retinopathy status at first screening R1	R2 Level Number, Cumulative incidence (95% CI)	R3 level Number, Cumulative incidence (95% CI)	Maculopathy M1 Number, Cumulative incidence (95% CI)	Cumulative incidence of sight threatening diabetic retinopathy per year of follow-up (95% CI)
Stratton *et al.* [21]	656	Mild NPDR ETDRS 20-35	27 4.12 (2.8-5.9)	1 0.15 (0.0-0.9)	–	0.71 (0.3-1.7)
Cikamatana *et al.* [25]	39	Questionable, minimal and mild NPDR ETDRS 14-35	5 12.8 (6-27) ETDRS 47	0 0 (0-9)	–	2.6 (1.5-13.6)
Song *et al.* [5]	1,387	Mild NPDR ETDRS 20-35	81 5.84 (4.7-7.2) ETDRS > 43	5 0.36 (0.2-0.8)	–	1.55 (1.0-2.4)
Scanlon *et al.* [20]	6,553	Mild NPDR ETDRS 20-35	542 8.27 (7.6-9.0) R2 or R3	34 0.52 (0.4-0.7) R3	878 13.4 (12.6-14.2)	6.53 (6.0-7.2)
Van der Heijden *et al.* [23]	302	Mild NPDR ETDRS 20-35	27 8.9 (6.2-12.7) ETDRS > 43		–	1.99 (0.9-4.3)

ETDRS, Early treatment diabetic retinopathy study; NPDR, Non-proliferative retinopathy; PDR, Proliferative retinopathy; STDR, Sight threatening diabetic retinopathy.

The incidence rates were reported in eight studies (Tables 2 and 3). In the other nine studies, cumulative incidence was used as the outcome measure (Tables 4 and 5). Incidence rate is the most precise estimate of incidence. Cumulative incidence has an unknown dropout rate.

The STDR incidence rates of people without retinopathy at last screening session varied from 0.27 [3] to 1.5 [4] per 100 person-years (Table 2). The studies reported different types of STDR, therefore, results are only partially comparable. Three-dimensional maculopathy was not taken into account in the ETDRS classification and was not always recorded.

The rate of progression to STDR in people with only mild diabetic retinopathy at last screening session was substantially higher. The incidence rate varied from 5.1 [7] to 9.9 [18] (Table 3).

The mean yearly cumulative incidence of people without retinopathy at last screening session varied from 0.08 [19] to 1.04 [20] (Table 4). People with only mild retinopathy at last screening session had cumulative incidences from 0.72 [21] to 6.5 [20] (Table 5).

Numbers needed to screen

In six studies the number of screening sessions was available and for these studies we calculated the number of individual screening sessions needed to detect one case of R3; R2 or R3; M1 or STDR (Tables 6 and 7).

Proliferative retinopathy was detected at only one in ~2000 screening sessions in people without diabetic retinopathy at last screening session. Proliferative retinopathy is always an indication for immediate referral to an ophthalmologist. Detection of maculopathy occurs more frequently; ~300 screening sessions are needed to detect maculopathy in people without diabetic retinopathy at last screening session. In people with mild diabetic retinopathy at last screening session, the screening yield is considerably higher than in people without diabetic retinopathy. The numbers needed to screen were 19 and 175 in people with and without diabetic retinopathy, respectively (Tables 6 and 7).

Discussion

Strengths of the present review include the fact that it provides a representative overview of diabetic retinopathy screening, based on large and global populations of people with Type 2 diabetes. Seventeen studies in 13 countries on four continents were included, and participants comprised totals of 326 112 people without any retinopathy and 48 610 people with only mild retinopathy. In addition, the review outcomes are of great relevance. There is an ongoing debate about the optimal screening interval for diabetic retinopathy. Up-to-date information on representative retinopathy incidence is crucial for confirmation and development of screening procedures.

The study also has some limitations. First, the inclusion criteria of the described cohort studies were different and probably had an effect on the outcomes of these studies. In studies focusing on people without retinopathy at baseline, people with existing diabetic retinopathy were excluded; therefore, the included participants in these studies were presumably healthier and more resistant to development of

Table 6 Number of people with Type 2 diabetes without diabetic retinopathy at baseline, number of screening sessions, and number needed to detect one person with sight-threatening diabetic retinopathy with and without maculopathy

Number of events and number ofscreeningsessions					Outcome			
Author	Participants with PDR* (R3)	Participants with severe NPDR or PDR* (R2 or R3)	Participants with maculopathy (M1)	Total number of screening sessions with 1–1.5-year interval	Number of screening sessions needed to detect one case of PDR* (R3)	Number of screening sessions needed to detect one case of severe NPDR or PDR* (R2 or R3)	Number of screening sessions needed to detect one case of maculopathy (M1)	Number of screening sessions needed to detect one case of STDR
Younis et al. [18]	-	76	58	20.570	-	271	355	154
Thomas et al. [15]	28	151	197	93.069	3324	616	472	267
Jones et al. [14]	24	423	36	33.164	1382	78	921	74
Looker et al. [7]	-	282	1605	300.817	-	1067	187	159
Liu et al. [3]	100 ETDRS ≥ 53	875[†] ETDRS 43–53	-	49.959	500 ETDRS ≥ 53	57[†] ETDRS 43-53	-	-
Martin-Merino et al. [27]			885	282.841	-	-	320	-
Weighted mean number of screening-sessions needed to detect one referable case					2158	782	313	175

ETDRS, Early Treatment Diabetic Retinopathy study; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; STDR, sight-threatening diabetic retinopathy. *Fast-track referral necessary. [†]Only R2.

microvascular complications than those excluded. The diabetic retinopathy incidence was not comparable between people with an unknown duration of Type 2 diabetes without retinal screening on one hand and people receiving intermittent retinal screening on the other hand.

Second, none of the included studies present data on the final diabetic retinopathy diagnosis by an ophthalmologist after referral, therefore, the accuracy of the screening results is uncertain; however, comparison of classification errors made by diabetic retinopathy screening service graders and errors made by hospital eye service doctors showed more

over-gradings in the screening service and more under-gradings in the hospital service [33].

Third, maculopathy, a tri-dimensional sight-threatening abnormality, was not always reported in the included studies and may have been missed by photography. If reported, maculopathy forms the bulk of STDR incidences [7,20,22]; therefore, availability of maculopathy data influences the STDR results significantly.

Fourth, because of unknown drop-out numbers in the studies, cumulative incidence was possibly underestimated; however, all people were screened at least twice, thereby meeting the study

Table 7 Number of people with Type 2 diabetes with mild diabetic retinopathy at baseline, number of screening sessions, and number needed to detect one person with sight-threatening diabetic retinopathy with and without maculopathy

Author	Participants with PDR* (R3)	Participants with severe NPDR or PDR (R2 or R3)	Participants with maculopathy (M1)	Total number of screens with 1–1.5-year interval	Number of screening sessions needed to detect one case with PDR (R3) (fast-track referral necessary)	Number of screening sessions needed to detect one case with severe NPDR or PDR (R2 or R3)	Number of screening sessions needed to detect one case of maculopathy	Number of screening sessions needed to detect one case of STDR
Younis et al. [18]	-	150	127	1,845	-	12.3	14.5	6.7
Jones et al. [14]	37	889	103	8,240	223	9.3	80	8.3
Looker et al. [7]		808	4,457	104,133	-	129	23	19.8
Weighted mean number of screening sessions to detect one referable case						118	27	18.9

NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; STDR, sight-threatening diabetic retinopathy.
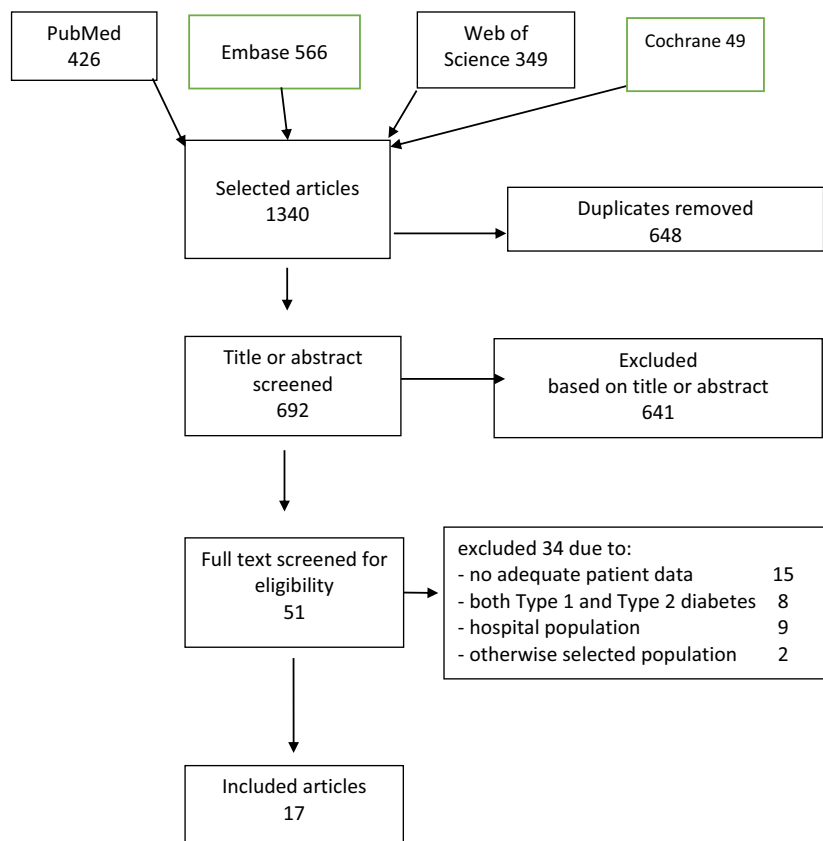
FIGURE 1 Flow diagram of sources and numbers of included papers.

selection criteria of the present review. Durations of the included studies were quite short, and cumulative incidences and incidence rates did not differ significantly.

Fifth, classification of diabetic retinopathy is a challenging task and different scales and grading protocols were used among the different populations [34]. In one study maculopathy was only diagnosed if the visual acuity of the affected eye was <0.5 [20]. Commonly used terms, such as 'referable' and 'observable' are not uniformly defined, even in most national retinopathy screening guidelines. We equated 'referable' diabetic retinopathy with STDR. Moreover, there will be differences in interpretation and judgement [35]. Misclassification may have occurred, particularly because interpretation of fundus photographs is equivocal.

In summary, the two main findings of the present review are important to consider when verifying and developing retinopathy screening guidelines in people with Type 2 diabetes. First, the incidence of STDR with no pre-existing retinopathy was low. Studies suggest that there is an overall downward trend in incidence [10–12]. Second, the incidence rate for STDR in people with pre-existing mild retinopathy is almost 10-fold higher than in people without retinopathy at last screening session.

The implications of these findings are also twofold. First, we suggest that the screening interval for people with Type 2

diabetes without retinopathy should be widened. It is common to screen for retinopathy once every 1–3 years [16]. In nine of the studies included in the present review, the authors suggested that the screening interval for Type 2 diabetes without retinopathy at last screening session be extended [12–20]. We found three systematic reviews focusing on the effect of screening intervals on the incidence of STDR and visual loss [28–30]. One of these studies reported insufficient evidence to change the screening interval [28]; however, two studies concluded that a 2-year screening interval for people with no diabetic retinopathy at baseline may be safely adopted instead of a 1-year screening interval [29,30]. An extensive Health Technology Assessment concluded that a 3-year screening interval for all people with diabetes is most likely to be cost-effective [31]. More recently, Sabanayagam *et al.* [32] published a systematic review of the incidence of STDR in Type 2 diabetes. They found similar cumulative incidence of proliferative retinopathy and progression. Our searches hardly found any overlap in selected papers. The narrow focus of the present review on population-based, systematic retinopathy screening of people with Type 2 diabetes, without or with only mild retinopathy makes our results more specific for assessment of screening guidelines for the majority of people with Type 2 diabetes.

Other than the low incidence of STDR in screening of people with Type 2 diabetes without retinopathy at

baseline, there are several other, but related, reasons to argue for the widening of the retinopathy screening interval for people without pre-existing retinopathy. Firstly, severe diabetic retinopathy in Type 2 diabetes is uncommon and develops slowly; therefore, it is very unlikely that development of non-proliferative retinopathy to severe or proliferative retinopathy will occur within 3 years if there are no signs of retinopathy at last screening session. Secondly, regular screening for retinopathy is time-consuming and expensive for people with Type 2 diabetes and for the healthcare system. Reduction of the number of screening sessions reduces the impact on people with Type 2 diabetes and the health system. Moreover, annual screening for diabetic retinopathy is associated with a disproportionate number of false-positive results or over-referrals [31]. In light of this, evidence-based revision of the screening interval for people without retinopathy at last screening-session is desirable.

The second implication of the present review is that an adapted screening interval for people with only mild retinopathy at last screening session is useful. As progression is slow and regression is common in screen-detected mild retinopathy, referral is not necessary for people with only mild retinopathy. Instead, continuing the screening with an interval of 1 year is adequate to observe progression.

Future research should include use of the personal and disease characteristics of people with diabetes, screening data and definitive ophthalmic retinopathy diagnosis. This will help to optimize the screening interval for diabetic retinopathy.

In conclusion, in people with Type 2 diabetes without retinopathy at last screening session, incidence and progression to STDR was low. Widening of the screening interval is possible. In people with Type 2 diabetes with only mild retinopathy at last screening session, progression to STDR was significantly higher. These two findings should be considered in the development of national guidelines for diabetic retinopathy screening.

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Competing interests

None declared.

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